REMARKS

Paragraphs [0049] and [0079] of the Specification have been amended to delete embedded hyperlinks and to properly designate a trademark.

Claim 4 has been revised to correct a typographical error.

Claim 5 has been canceled.

Claims 6 and 11-14 have been withdrawn from consideration by the Examiner.

No new matter has been introduced, and entry of the revised claims is respectfully requested.

Objections to the Specification

The Action objects to the specification because it contains embedded hyperlinks and/or other forms of browser executable code and because the trademark TWEEN is not capitalized or denoted with the registered trademark symbol. Paragraphs [0049] and [0079] of the specification have been amended to delete the referenced embedded hyperlink and to properly designate TWEEN in all capital letters. Applicants respectfully submit that with these corrections, the objections may be properly withdrawn.

Claim Objections

The Action advised that should claim 5 be found allowable, claim 7 would be objected to under 37 C.F.R. §1.75 as being a substantial duplicate of claim 5. Claim 5 has been canceled, and so this objection is believed to be moot and may be properly withdrawn.

Alleged Rejections under 35 U.S.C. §103(a)

The Action rejects claims 1-5 and 7-10 as allegedly obvious in light of Whitelam (J. Sci. Food Agric., 1995, 68:1-9) in combination with each of Stiens et al. (Biotechnol. Prog., 2000, 16:703-709), Mullins et al. (J. Clin. Invest., 1995, 96:30-37) and Takeo et al. (EP 0719 858 A2 (1996)). So this rejection is essentially three rejections, based on Whitelam and Stiens et al.; Whitelam and Mullins et al.; and Whitelam and Takeo et al.

The Action asserts that because Whitelam reports the recombinant expression of certain polypeptides in plants, it would be obvious to use those methods to recombinantly express hTSHR (human thyroid stimulating hormone receptor) as reported by each of the other three documents.

Applicants have reviewed the statement of rejection and respectfully traverse because no *prima facie* case of obviousness is present. Reconsideration and withdrawal of this rejection are respectfully requested.

One of skill in the art would not have had a reasonable expectation of success in combining these references. As an initial matter, it must be noted that hTSHR is an animal protein, and each of the three documents cited in combination with Whitelam, namely, Stiens et al., Mullins et al., and Takeo et al., only report the production of hTSHR produced in mammalian cells (human leukemia cells, B-cells and myeloma cell line cells, respectively).

The use of mammalian cells reported by Stiens et al., Mullins et al., and Takeo et al. is significant. Stiens et al. report in its Abstract that

> For the detection of autoantibodies to thyroid stimulating hormone receptors (TSH-R) in Graves' disease based on a novel coated tube assay system, human

> TSH-R is needed in large amounts. Whereas expression of TSH-R in bacteria, yeast, or insect cells results in nonfunctional, denaturated receptor, mammalian cells such as COS, CHO, and HeLa are able to express functional TSH-R, but only in very low amounts. Furthermore, for all of these cultivations expensive standard media containing 10% fetal calf serum are needed to obtain functional receptor. Here we report on the development of a serum-free production-scale process based on a stable transformed and highly productive human leukemia cell line K562 [].

Thus attempts to use different systems such as bacteria, yeast and insect cells to produce large amounts of TSHR with functional receptors have failed, and those of skill in the art have turned to mammalian expression systems. Consequently, there would simply be no reasonable expectation of success in using a non-mammalian system, such as those in the claimed invention, for the expression of TSHR with functional receptors, particularly when it is known that non-mammalian systems pose difficulties, e.g., non-functional and denatured receptors.

Indeed, Stiens et al., Mullins et al., and Takeo et al. all teach away from the use of a plant-based system because each and every one of these documents report the production of a mammalian protein in mammalian cells. And despite the fact that Whitelam reports on "The Production of Recombinant Proteins in Plants," that would not motivate one of ordinary skill in the art to attempt to express *every* animal protein in *any* plant-based system. Indeed, the instant rejection appears to be based upon an improper "obvious to try" standard, which even if applied, must be accompanied by a reasonable expectation of success.

Additionally, extending the arguments in the instant rejection to encompass every animal protein in any plant-based system would be unreasonable given the knowledge in the art, when the difficulties surrounding expression of an animal protein in non-mammalian cells have been reported and documented.

The lack of success in the prior art argues in favor of the patentability of the present invention. Applicants have successfully transformed plants with the hTSHR or hTSHR-ECD

genes, and the proteins produced from these plants possess a high antigen affinity. *See* Example 5 and Figure 7 in the Specification. The high antigen affinity is an unexpected result given the problems associated with the use of non-mammalian systems, which Stiens et al. report result in nonfunctional, denatured receptors. This surprising result further supports the conclusion that the present invention is not obvious.

The results further distinguish the instantly claimed invention from that of the cited references, especially Whitelam, which reports the need for oleosin as a carrier to improve yields from recombinant expression in plants. The instant invention sidesteps this need and so provides an additional indication that the claimed methods are non-obvious.

In light of the above, there is no motivation or suggestion that leads a combination of the documents to the subject matter encompassed by the instant claims, nor would there be a reasonable expectation of success in the combinations. Mullins et al., Takeo et al., and especially Stiens et al. teach away from the use of non-mammalian expression systems and therefore teach away from the instant claims. Furthermore, the unexpectedly high antigen affinity in the disclosure is an unexpected result. For all of these reasons, no *prima facie* case of obviousness is present, so this rejection is misplaced and may be properly withdrawn.

Conclusion

It is believed that the application is now in condition for allowance. Applicants request the Examiner to issue a notice of Allowance in due course. The Examiner is encouraged to contact the undersigned to further the prosecution of the present invention.

The Commissioner is authorized to charge JHK Law's Deposit Account No. **502486** for any fees required under 37 CFR § 1.16 and 1.17 and to credit any overpayment to said Deposit Account No. **502486**.

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